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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/361,576	07/27/1999	BRENT R. STOCKWELL	2001180-0028	5706

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EXAMINER	
FRIEND, TOMAS H F	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 12/18/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
file copy	09/361,576	STOCKWELL ET AL.	
	Examiner	Art Unit	
	Tomas Friend	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-103* is/are pending in the application.

4a) Of the above claim(s) *84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-83 and 85-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Change of Art Unit Designation

Please note: The Art Unit location of this application in the PTO has changed from Art Unit 1627 to Art Unit 1639. To aid in matching papers to this application, all further correspondence regarding this application should be directed to **Group Art Unit 1639**.

Status of the Application

A response to an election of species requirement was received on 15 October 2002 (Paper No. 26).

Status of the Claims

The examiner acknowledges applicants' comments regarding the numbering of the claims in view of the non-entry of claims 57-81 in the advisory action mailed 05 April 2002. The request for continued examination was submitted together with the amendment canceling claims 57-81 and adding new claims 82-128. Accordingly, the office did not enter (or cancel) claims 57-81. New claims 82-128 were renumbered 57-103 because the entry of these claims occurred without the prior entry of claims 57-81. Claims 81-128 as added in Paper No. 23 remain renumbered 57-103. The examiner regrets any inconvenience that this may cause applicants.

Claims 57-103 are pending in the present application. Claim 84 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Claims 57-83 and 85-103 are pending in the present application and examined on their merits.

Withdrawn Rejections

All rejections of record are withdrawn in response to the cancellation of all pending claims.

Response to Election of Species

Applicant's election without traverse of antibody as species of ligand and second ligand, 5-bromodeoxyuridine as species of reagent, and one as species of number of different cell lines used in Paper No. 26 is acknowledged.

Claims Rejections – 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 57-83 and 85-103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claims 57 and 58, it is not clear if a ligand "*characterized by an ability to associate intracellularly with a biological component*" is intended to mean that the ligand does bind intracellularly when using the claimed method, or if the ligand may bind extracellularly as long as it has the ability (under non-specified conditions) to bind a biological component intracellularly.

B. Claim 62 recites a limitation on a "*third ligand,*" which is not required in claim 58 from which claim 62 depends.

C. Claim 66 recites the limitation that the secondary ligand is assayed intracellularly. It is not clear how this further limits claims 64 and 65 because the first ligand to which the secondary ligand is bound appears to be present intracellularly. Clarification is requested.

D. In claim 72, it is not clear if the "*one reagent known to exert an effect*" on the process excludes a test compound or a nutrient required or otherwise normally used for culturing a cell, for example. Clarification is requested.

E. In claim 78, the "*intracellular biological reaction*" is limited by a Markush listing that includes "*an intracellular biochemical reaction.*" The difference between an "*intracellular biological reaction*" and an " *intracellular biochemical reaction*" is not clear.

F. It is not clear how claim 82 further limits claim 79 since only proteins are made by translation and claim 79 recites a post-translational event.

G. It is not clear how claim 88 further limits claims 57 and 58 because one skilled in the art would not know of a compound that is neither natural nor synthetic.

H. In claims 95-98, the limitation with respect to density of reaction vessels cannot be interpreted without any specified arrangement of vessels relative to one another. The densities would be measured differently for a 2-D array vs. a one-dimensional array, for example.

Claims Rejections – 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

2. Claims 57-62, 69-78, 83, 85-88, 102, and 103 are rejected under 35 U.S.C. 102(e) as being anticipated by Walsh, U.S. Patent 5,990,092 (November 1999).

The Walsh patent, Example 4, discloses an in vitro assay for selecting GATA-6 molecules that modulate vascular smooth muscle proliferation. Column 28, lines 28-44, discloses that A7r5 cells (rat) are cultured in media containing the test molecule for up to 72

hours. The cells are harvested at various time points and the proliferative state of the cells is determined by immunohistochemical assays including a BrdU assay and a proliferating cell nuclear antigen (PCNA) assay (i.e. an assay for an intracellular antigen). Column 28, lines 47-51, discloses that cells are fixed onto a tissue culture dish (reaction vessel), dried, and immunostained using a monoclonal antibody to PCNA (i.e. first ligand). Column 27, lines 13-25, discloses that the BrdU assay involves adding BrdU (a reagent known to exert an effect on the process of proliferation) to growth media (containing the cells to be tested) for 24 hours, fixing and permeabilizing the cells, and identifying proliferating cells with a mouse anti-BrdU antibody coupled to FITC (i.e. a second ligand coupled to a fluorescent tag). One of skilled in the art would know that washing steps to remove unbound antibody are inherently a part of immunostaining assays. Accordingly, the Walsh reference anticipates present claims 57-62, 69-78, 83, 85, 86, 88, 102, and 103.

One skilled in the art would have immediately envisaged the use of a human cell line, anticipating present claim 87.

3. Claims 57, 59-61, 64, 66, 67, 69, 71-74, 76-79, 81-83, 85-88, 102, and 103 are rejected under 35 U.S.C. 102(b) as being anticipated by Photiou et al. European Journal of Cancer 33(3):463-470 (March 1997).

The Photiou et al. reference discloses a method for evaluating the in vitro antiproliferative activity (inhibiting cell replication and therefore DNA synthesis) of drugs as single agents and as combinations using human melanoma cell lines G361 and StMl11a (abstract). Page 465, column 1, discloses an indirect immunofluorescence method in which cells are seeded on glass coverslips placed in 24-well plates, treated with drug(s), fixed, permeated, incubated with rabbit anti-tubulin antibodies, washed, and incubated with goat anti-rabbit antibody conjugated to FITC. Page 466, columns 1 and 2, discloses the interpretation of the tubulin immunofluorescence data, including the intracellular localization of the primary and secondary antibodies. The prevention of tubulin polymerization is a "post-translational event" and an "intracellular biochemical reaction." Accordingly, the Photiou et al. reference anticipates present claims 57, 59-61, 64, 66, 67, 69, 71-74, 76-79, 81-83, 85-88, 102, and 103.

4. Claims 57-62, 64-67,69-83, 85-88, 102, and 103 are rejected under 35 U.S.C. 102(a) as being anticipated by Juan et al. Experimental Cell Research 239:104-110 (February 1988).

The Juan et al. reference discloses a method for monitoring the phosphorylation status of the retinoblastoma susceptibility gene product (protein) pRb, the phosphorylation of which is the key event committing the cell to enter the S phase of the cell cycle (abstract). Page 105 (Materials and Methods) discloses that human peripheral blood lymphocytes were treated with PHA to stimulate proliferation. The cells were assayed using one or more of three different antibodies by immunocytochemical methods. Fixed cells were incubated with anti-pRb^T mAb conjugated to Cy-Chrome and/or anti-pRb^{P-} mAb conjugated to FITC. In addition, fixed cells were incubated with anti-cyclin D3 mAb, washed, and incubated with FITC-conjugated goat anti-mouse IgG antibody. Page 109, column 1, last paragraph, discloses that the assay "*can be conveniently used to rapidly screen activity*" of antitumor agents. Additionally, the reference discloses that the phosphorylation state of pRb can be correlated with DNA replication by detecting BrdU incorporation. Accordingly, the Juan et al. reference anticipates present claims 57-62, 64-67,69-83, 85-88, 102, and 103.

5. Claims 57-62, 64-67,69-83, 85-88, 102, and 103 are rejected under 35 U.S.C. 102(a) as being anticipated by Claycomb U.S. Patent No. 6,316,207 B1 November 2001 (PCT published May 1998).

The Claycomb patent discloses mouse cardiac cell line and associated cell culture system for testing cardiac drugs *in vitro* (abstract). Column 10, example 2, discloses that cells are labeled BrdU. Fixed cells are treated nuclease/anti-5-bromo-2'-deoxyuridine, washed, and incubated with peroxidase-conjugated anti-mouse antibody. The bound secondary antibody is developed using diaminobenzidine and visualized by the resulting blue-black staining. Column 6, lines 35-63, discloses that the cells are also assayed using primary antibodies to desmin and myosin heavy chain and secondary goat anti-mouse antibody conjugated to FITC. Accordingly, the Claycomb reference anticipates present claims 57-78, 82, 83, 85, 86, 88, 102, and 103.

Claims Rejections – 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims are 89-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one or more of Walsh, U.S. Patent 5,990,092 (November 1999); Photiou et al. European Journal of Cancer 33(3):463-470 (March 1997); Juan et al. Experimental Cell Research 239:104-110 (February 1988); Claycomb, U.S. Patent No. 6,316,207 B1 (November 2001) and the Final Conference Program of LabAutomation'98 held in San Diego, CA January 17-21, 1998, pages 99, 100, 124, 129, and 212.

The teachings of the Walsh, Photiou et al., Juan et al., and Claycomb references are described in the corresponding rejections under 35 U.S.C. 102 above and are incorporated herein in their entirety. The cited references do not explicitly teach test compounds from a combinatorial library, the release of test compounds from a solid support, or various capacities and densities of wells in well plates.

With respect to combinatorial libraries as test compounds as well as the release of test compounds from solid supports, it would have been obvious to one of ordinary skill in the art at the time that the invention was made to use members of combinatorial libraries as test compounds, including those made on solid supports which would require their release before testing. One would have been motivated to do so because combinatorial libraries were primarily synthesized as leads for drug development to be tested for biological activity and solid-phase synthesis was the most common method of combinatorial library synthesis practiced at the time.

With respect to particular numbers of wells, their capacities, and arrangements within a plate, for example, it would have been well within the abilities of one of ordinary skill to select well array formats from those commonly sold for the purpose of high throughput screening as described ion pages 99, 100, 124, 129, and 212 of the Final Conference Program of

LabAutomation'98, which include 1536-well, 384-well, 96-well, and 10,000-well formats, for example. Well volumes and spacings include 12 microliters and 2.25 mm, for example.

Conclusion

7. No claims are allowed.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Tomas Friend** at telephone number **(703) 308-4548**. The examiner works on a flexible schedule of four ten-hour days per week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Tomas Friend, Ph.D.
14 December 2002